TITLE PAGE

Placental growth factor (PlGF) as an indicator of fetal growth restriction in late-onset small for gestational age pregnancies.

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Placental growth factor (PlGF) as an indicator of fetal growth restriction in late-onset small for gestational age pregnancies.

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Abstract

Background: At-risk small-for-gestational age (SGA) pregnancies in New Zealand are identified using Doppler ultrasound; fetuses with Doppler abnormalities are considered growth restricted (FGR). Low maternal PlGF has also been associated with late-onset FGR.

Aims: Investigate whether low PlGF at diagnosis of late-onset SGA identifies the same fetuses classified FGR by detailed Doppler studies, and the association between low PlGF and adverse pregnancy outcomes.

Methods: Among an historical database of normotensive suspected SGA pregnancies (fetal abdominal circumference <10th%ile) ≥32 weeks' gestation, the ability of low PlGF (<5th%ile) to identify FGR infants was investigated. 'Initial FGR' was an abnormal umbilical artery resistance index (RI) or estimated fetal weight <3rd customised centile. 'Secondary FGR' was abnormal internal carotid RI, cerebro-placental ratio and/or mean uterine artery RI. Development of hypertensive disease and adverse perinatal outcomes were compared by PlGF status.

Results: Of 136 SGA pregnancies, 56 (41.1%) had initial FGR. Of the remaining, 20 (25.0%) had secondary FGR, 17 (21.3%) low PlGF. The sensitivity of low PlGF identifying secondary FGR was 0.30 (95% CI 0.14-0.50), specificity 0.83 (0.70-0.92), positive predictive value 0.47 (0.23-0.72), negative predictive value 0.70 (0.57-0.81). Overall, low PlGF occurred in 44/136 (32.4%) pregnancies and was associated with gestational hypertensive disease (63.6% cf 15.2%, p<0.01), adverse perinatal outcome (34.1% cf 15.2%, p=0.01) and very low birthweight (customised centile 2.2 cf 6.8, p<0.01).

Conclusions: At diagnosis of late-onset SGA, low PlGF was poor at identifying Doppler-defined FGR. Low PlGF identified pregnancies at risk of hypertensive disease, adverse perinatal outcome and very low birthweight.

Introduction

Fetuses with suboptimal growth due to utero-placental insufficiency are at increased risk of adverse consequences ranging from poor perinatal outcomes to abnormal neurodevelopment and long term cardiovascular risk.[1,2] One of the main challenges of antenatal care is to identify at-risk fetuses to enable optimum surveillance and timely delivery, without intervening in pregnancies where the fetus is small but otherwise well.

Fetal growth restriction (FGR, a failure of a fetus to reach its biological growth potential because of placental dysfunction) is suspected when an ultrasound estimated fetal weight (EFW) or abdominal circumference (AC) is less than the 10th percentile, or serial ultrasound examinations suggest slowing of growth velocity.[3] Among small for gestational age fetuses (SGA, EFW <10th centile), umbilical artery (UA) Doppler studies are routinely performed, but in the case of late-onset SGA (>32 week's gestation) UA Doppler is commonly normal.[4,5] Additional Doppler studies of fetal cerebral and maternal uterine artery vascular resistance can however identify late-onset SGA pregnancies at-risk of adverse perinatal outcome.[4-8] These include fetuses with an increase in fetal cerebral blood flow (including a reduction in the ratio of cerebral to umbilical artery Doppler indices i.e. a low cerebro-placental ratio, CPR), and pregnancies with high uterine artery vascular resistance.

Abnormal maternal and/or fetal Doppler studies are associated with placental pathology resulting from impaired placental angiogenesis.[9,10] Placental angiogenic biomarkers present in the maternal circulation are indicators of placental function and therefore potential predictors of FGR. While alterations in early pregnancy biomarkers can predict early-onset placental-mediated disease (pre-eclampsia and FGR), prediction of late-onset FGR is poor despite 70-80% of FGR occurring late in gestation.[11,12] When performed in the third trimester, the ability of biomarkers to identify placental mediated complications increases when used in high-risk populations, e.g. among suspected SGA fetuses.[13-15] Among late-onset SGA pregnancies, low maternal placental growth factor (PlGF) identifies with high sensitivity FGR pregnancies with significant placental pathology.[16] Low PlGF measured at the diagnosis of a small fetus may therefore be a promising antenatal discriminator between FGR and constitutionally small fetuses.

In New Zealand (NZ), late-onset SGA fetuses with features of FGR (i.e. abnormal UA, CPR, UtA Doppler or EFW < 3rd customised centile) are considered high risk and guidelines recommend increased surveillance and early-term delivery.[17] Fetuses without features of FGR are expectantly managed until 40 weeks' gestation. While this ultrasound definition of FGR is consistent with international best practice,[3,18] serial Doppler ultrasound examinations may not be available in some NZ centres.

Among late-onset SGA pregnancies, we aimed to explore the relationship between low PlGF (<5th percentile) and FGR defined by ultrasound (EFW <3rd centile and/or abnormal Doppler studies). We hypothesised that a low PlGF at diagnosis of suspected SGA would identify similar FGR pregnancies as ultrasound. Additionally, among SGA pregnancies without features of FGR on initial ultrasound, we aimed to determine whether low PlGF would identify the same FGR pregnancies as serial

Doppler measurements. Our secondary aim was to investigate the relationship between low PlGF and adverse pregnancy outcomes, including adverse perinatal outcome (operative delivery for fetal distress and/or evidence of birth asphyxia) and the development of gestational hypertensive disease.

Methods

Prospectively collected data were used from an historical database of suspected SGA pregnancies in Auckland, New Zealand (Ethics approval NTX/11/056/02 Northern Regional Ethics Committee).[19] Women were recruited between 1993 and 1997 if they had a singleton pregnancy with ultrasound evidence of suspected SGA (AC <10th percentile) and no evidence of fetal abnormality. UA Doppler resistance index (RI) was performed on entry into the study. After recruitment, additional Doppler studies were performed (including UA RI, internal carotid artery (ICA) RI and UtA RI), and growth scans were performed at two weekly intervals until birth. Ten mL of maternal venous blood was taken within two weeks of recruitment.

Women were excluded if they were hypertensive at the diagnosis of SGA, <32 weeks' gestational age at the time of blood sampling, had incomplete data on UA Doppler or EFW, or if there was more than two weeks between ultrasound fetal biometry and blood sampling, Figure 1.

Management of the pregnancy was continued by the referring clinician, with a decision for delivery based around clinical indicators at the time. This included the recommendation that in the absence of other concerns regarding fetal wellbeing, delivery should not be undertaken on the basis of abnormal Doppler studies. Detailed demographic, antenatal, labour and birth data were collected by a research

midwife, including any fetal indication for induction of labour, operative delivery for fetal distress, or neonatal complications.

Definitions

Ultrasound scans and Doppler studies were performed by trained sonographers in a clinical ultrasound department using a Diasonics Masters Series (Diasonic, California, USA) or Toshiba 270 (Toshiba Medical Systems, Tokyo, Japan) ultrasound machine. Doppler studies were performed with the patient semi-recumbent during fetal quiescence and apnoea. Mean RI was calculated from five waveforms. UA Doppler studies were considered abnormal if greater than the 95th percentile,[20] and ICA Doppler studies were considered abnormal if the RI was less than the 10th percentile for gestational age.[21] Mean RI of the right and left UtA was recorded and considered abnormal if greater than the 95th percentile for gestational age.[20] CPR was defined as the ratio between the ICA and UA Dopper RI and considered abnormal if the ratio was less than the 10th percentile.[22,23]

EFW was calculated from fetal biometry using the Hadlock 4 equation.[24] EFW centiles were customised accounting for gestational age, maternal height, weight, parity and ethnicity. If maternal height or weight was unknown, NZ population median values for ethnic group were used.[25]

At recruitment, SGA pregnancies with high-risk features on initial scan (EFW less than the 3rd customised centile, or abnormal UA Doppler study[18]) were classified as 'initial FGR'. SGA pregnancies with high-risk features on subsequent scanning (abnormal ICA RI, CPR, mean UtA RI or UA RI) were classified as 'secondary FGR'.

Maternal venous blood was collected by a research midwife using 10mL EDTA plasma tubes, allowed to clot at 37C for one hour and then centrifuged at 2000 rpm

for 10 minutes before storage at -80C. Samples were subsequently patch assayed for PlGF using an automated immunoassay (Triage®, Alere, San Diego, CA, USA). Low PlGF was defined as a concentration <5th percentile for gestational age.[26]

Gestational hypertension was a diastolic blood pressure ≥90 mmHg on more than two occasions at least 6 hours apart and pre-eclampsia was gestational hypertension with proteinuria of 2+ on dipstick or >0.3g/ 24h.[27]

Detailed labour and perinatal outcomes were collected prospectively by a research midwife. Operative delivery for fetal distress included Caesarean section (CS) or instrumental delivery with an abnormal scalp pH (<7.25) or major fetal heart rate abnormality on cardiotocograph monitoring. Adverse perinatal outcome was a composite of operative delivery for fetal distress and/or evidence of birth asphyxia (cord arterial pH <7.15 and base deficit >7 mEq/L, and/or Apgar score at 5 minutes <7).[19]

Statistics

Student's *t*-test or the Mann-Whitney *U*–test and Chi-square or Fisher's exact test were used as appropriate. P-values of <0.05 were considered significant. Normally distributed data were reported using means with standard deviations, while non-normally distributed data using medians with interquartile ranges. Categorical data were reported using counts and proportions.

Sensitivity, specificity, positive and negative predictive values of PlGF <5th centile describing FGR were calculated with 95% confidence intervals.

Statistical analysis was performed using SAS© 9.4 (Cary, NY, USA).

Results

We identified 259 women with SGA pregnancies and maternal serum samples. After exclusions, the initial study population included 136 women, Figure 1. Participants were enrolled at a mean gestational age of 33.3 (SD 1.7) weeks, with a median time between diagnosis of suspected SGA and PlGF test of 1.4 weeks. Women were predominantly European (59.6%), nulliparous (53.7%) and over a third were smokers (36.8%). Baseline and clinical characteristics of the study population are displayed in Table 1. Data were missing for cerebral Doppler studies (ICA / CPR) in ten pregnancies, and UtA Doppler studies in two pregnancies.

Of the 136 SGA pregnancies, 56 (41.2%) had initial FGR (EFW <3rd centile n=50, abnormal UA RI n=22) while 27 (19.9%) subsequently met criteria for secondary FGR. A low PlGF was identified in 44 (32.4%) pregnancies. Overall FGR (initial or secondary) was more common among those with a low PlGF (79.6% vs. 52.2% p<0.01, Table 2). The sensitivity of PlGF <5th centile identifying FGR was 0.42 (95% CI 0.31-0.54), specificity 0.83 (0.70-0.92), positive predictive value (PPV) 0.80 (0.65-0.90) and negative predictive value (NPV) 0.48 (0.37-0.59).

Women with low PlGF had high rates of subsequent gestational hypertensive disease (63.6%) with all cases of pre-eclampsia occurring in this group, Table 2. At birth, two thirds of low PlGF pregnancies had a birthweight <3rd customised centile, and one third of low PlGF pregnancies experienced an adverse perinatal outcome; double the rate of the normal PlGF group, Table 2. While there were no significant differences by PLGF status in Caesarean section prior to the onset of labour, (low PlGF 13.6% vs. 5.4%, p = 0.07), rates of 5 minute Apgar score <7 (low PlGF 4.6% vs. 1.1%, p=0.21) or cord gas acidosis (low PlGF 4.6% vs. 2.2%, p=0.29), there was

a non-significant trend towards more severe outcomes among the low PlGF group. The lack of significance of these results may be due to the small numbers in the study.

As initial FGR pregnancies were identified as high risk at SGA diagnosis, we investigated the role of PlGF to identify secondary FGR, i.e. FGR identified on subsequent scanning. Of 80 pregnancies, secondary FGR was diagnosed in a third (n=27, 33.8%; abnormal UtA RI n=16, UA RI n=8, ICA RI n=8, and CPR n=6) and a low PlGF was identified in 17 (21.3%). There were no significant differences in secondary FGR by PlGF status, however there was again a trend towards a higher proportion of secondary FGR among the low PlGF group (low PlGF 47.1%, normal PlGF 30.2%, p = 0.19, Table 3). The sensitivity of PlGF <5th centile identifying secondary FGR was 0.30 (95% CI 0.14-0.50), specificity 0.83 (0.70-0.92), PPV 0.47 (0.23-0.72) and NPV 0.70 (0.57-0.81).

Similar to the initial study population, pregnancies with low PlGF in the secondary study population were more likely to experience gestational hypertensive disease (low PlGF 58.8%, normal PlGF 12.7%, p<0.01) and were more likely to be SGA at birth (low PlGF 88.2%, normal PlGF 54.0%, p=0.01), Table 3. There were no differences in adverse perinatal outcome, but numbers were low.

Sensitivity analyses were performed, excluding those with missing ICA and/or UtA Dopplers (n=11). No differences in statistical significance were seen, and negligible differences in test performance characteristics were observed.

Discussion

In this historical cohort of late-onset SGA pregnancies, low PlGF identified pregnancies that were at risk of both severe growth restriction and adverse perinatal outcome, predominantly due to operative delivery for fetal distress. Low PlGF therefore identified a more severe FGR phenotype associated with poor placental function and subsequent intolerance of labour, consistent with the association previously seen between low PlGF and placental FGR.[16] Low PlGF was also strongly associated with the later development of gestational hypertensive diseases. However low PlGF did not reliably identify the same high-risk pregnancies as detailed Doppler ultrasound investigations. Low PlGF is therefore not an adequate replacement for serial detailed ultrasound Doppler measurements to identify high risk SGA pregnancies.

Only one study in a European cohort has investigated whether angiogenic placental biomarkers (including PlGF) in late-onset SGA can identify pregnancies at-risk of adverse outcome.[28] Among SGA pregnancies diagnosed on routine third-trimester ultrasound, they found that angiogenic biomarkers had a similar predictive value to serial Doppler indices in identifying high risk late-onset SGA pregnancies. Their analyses included SGA pregnancies with high-risk ultrasound features at initial evaluation (EFW <3rd centile or abnormal UA RI). We excluded these pregnancies in our analyses as these pregnancies are identified as high risk requiring additional surveillance regardless of PlGF result. In the remaining SGA pregnancies where FGR status is initially unknown, serial fetal Doppler interrogation is recommended and a single blood test to identify high-risk pregnancies would potentially be time- and cost-effective. However, our findings do not support the use of PlGF in this setting.

Low PlGF in late pregnancy has been shown to identify SGA pregnancies with significant placental pathology.[16,29] An abnormal UA RI is likewise associated with extensive vascular placental changes,[30] however a significant proportion of SGA pregnancies with normal umbilical artery Doppler studies also have histological evidence of poor placental perfusion.[31] We found that while pregnancies with an abnormal UA RI were more likely to have a low PlGF, 20% of pregnancies with an abnormal UA RI had a normal PlGF. This indicates a complex relationship between low PlGF, abnormal Doppler studies and placental pathology.

Our findings in a cohort of late-onset SGA pregnancies support the association between low PlGF and adverse pregnancy outcomes, including hypertensive disease.[28] In our cohort, over two thirds of pregnancies with low PlGF went on to develop gestational hypertension or pre-eclampsia, suggesting PlGF may be clinically useful among SGA pregnancies to identify those at greatest risk of subsequent hypertensive complications.

Ultrasound is a limited resource in NZ, particularly in regional areas where the skills required to perform uterine and fetal cerebral Doppler studies may not be available. Transfer to a secondary hospital for these examinations can be costly and time-consuming. Without access to serial detailed Doppler examination, elective delivery is recommended by 38-39 weeks' gestation,[17] which may be an unnecessary intervention in otherwise low risk SGA pregnancies. Unfortunately our data suggest that PlGF is not a substitute for more detailed Doppler investigations in SGA pregnancies.

Strengths

This cohort study had prospective collection of data including serial Doppler measurements linked with labour and birth outcome data and a biobank.

Limitations

As our data are historical, it is limited to what was collected and part of clinical practice at that time. Doppler studies at that time utilised RI instead of pulsatility index (PI), which is now considered best practice. Additionally, fetal cerebral blood flow was assessed using ICA Doppler, while currently middle cerebral artery (MCA) Doppler studies are standard. However, blood flow through the ICA is a surrogate for MCA blood flow and a CPR of <1 is independent of Doppler measurement type (RI vs PI) and is associated with increased perinatal risk.[23] In our population a CPR <1 identified the same pregnancies as a CPR <10th centile.

The management of SGA pregnancies at the time of data collection was not standardised. In particular an abnormal Doppler study didn't necessarily necessitate elective delivery, although increased surveillance was common. As a result, analysis of outcomes by FGR status would be misleading as it does not reflect current obstetric practice. We were therefore unable to include a comparison of outcomes between FGR and low PlGF pregnancies.

Overall this study had low numbers, particularly among our secondary study population. A larger sample size would have allowed for more robust evaluation of outcomes, however it is unlikely to have raised the test performance of PlGF to a point where it would be able to replace serial Doppler examinations.

Conclusion

We report that while low PlGF at the time of late-onset SGA diagnosis is associated with increased perinatal risk, it does not adequately identify at-risk FGR infants

classified using detailed Doppler studies. The measurement of PlGF in these women therefore cannot be considered an adequate replacement for serial Doppler investigations. Low PlGF is strongly associated with subsequent development of gestational hypertensive disease and therefore may be of clinical utility. Due to the historical nature of these data, our findings should be confirmed by repeating this analysis in a contemporary cohort.

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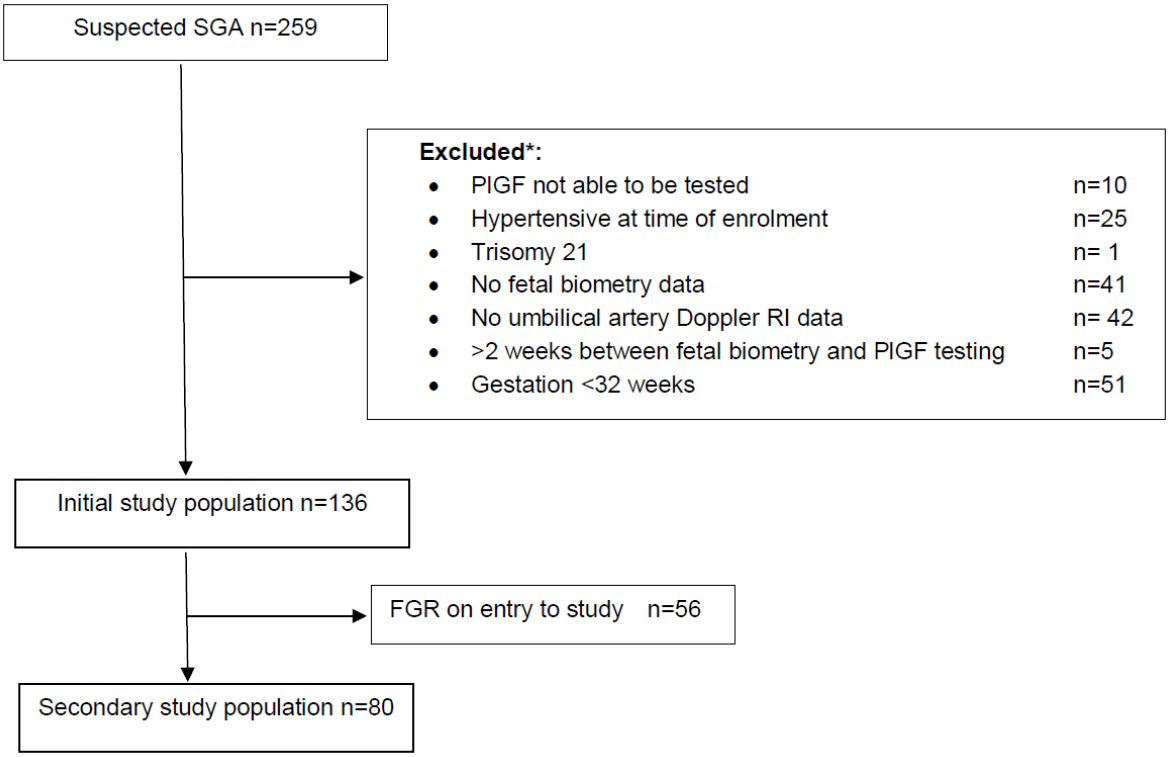
Figure 1: Flowchart of study population of women with suspected small for gestational age (SGA) pregnancies, defined as an abdominal circumference <10th centile. FGR, fetal growth restriction (abnormal umbilical artery Doppler resistance index and/or estimated fetal weight <3rd centile); PlGF, placental growth factor.

*more than one exclusion may apply so numbers do not total.



390 **Table 1:** Clinical characteristics of the full cohort study population (n=136)

Characteristic	**Value***
Demographics	
Age (y)	26.4 (5.3)
Weight† (kg)	63.1 (13.6)
Body Mass Index‡	22.5 (20.4-25.4)
Ethnicity	
European	81 (59.6%)
Maori	23 (16.9%)
Pacific	13 (9.6%)
Asian	16 (11.8%)
Other	3 (2.2%)
Nulliparous	73 (53.7%)
Smoker	50 (36.8%)
At enrolment	
Gestational age at enrolment (weeks)	33.3 (1.7)
Gestational age at PlGF measurement (weeks)	35.0 (1.5)
EFW customised centile	5.05 (1.5-10.8)
Maternal outcomes	
Gestational hypertension	34 (25.0%)
Pre-eclampsia	8 (5.9%)
Delivery outcomes	
Gestational age at delivery (weeks)	38.0 (1.7)
Preterm delivery (<37 weeks)	33 (24.3%)

IOL for fetal indication	96 (70.6%)
CS or instrumental delivery for fetal distress	25 (18.4%)
CS before labour for fetal distress	11 (8.1%)
Emergency CS in labour for fetal distress	7 (5.2%)
Instrumental delivery for fetal distress	7 (5.2%)
Birthweight (g)	2530 (479)
Birthweight customised centile	5.1 (2.0-11.9)
<10th customised centile	103 (75.7%)
<3rd customised centile	60 (44.1%)
Neonatal	
Apgar score <7 at 5 min	3 (2.2%)
Cord arterial blood gas acidosis	4 (2.9%)
NICU admission >48 h	33 (24.3%)
Adverse perinatal outcome§	29 (21.3%)

391 * mean (SD), median (IQR) or n (%) as appropriate

392 † n=27 missing

393 ‡ n=44 missing

394 § Adverse perinatal outcome: operative delivery for fetal distress and/or evidence of
395 birth asphyxia (cord arterial pH <7.15 and base deficit >7 mEq/L, and/or Apgar score
396 at 5 minutes <7).

397

398 EFW, estimated fetal weight; IOL, induction of labour; CS, Caesarean section; NICU,
399 neonatal intensive care unit

400 **Table 2:** Low PlGF and pregnancy outcome within the full cohort study population

401 (n=136)

	PlGF <5th centile N=44 (32.4%)	**PlGF>5th centile N=92 (67.6%)**	***P*-value**
Antenatal			
Gestational age at PlGF (weeks)	34.6 (1.4)	35.2 (1.5)	0.02
EFW (g)	1871 (321)	2130 (365)	<0.01
EFW customised centile	2.8 (0.6-6.4)	6.2 (2.4-11.8)	0.02
EFW <3rd customised centile	24 (54.6%)	26 (28.3%)	<0.01
Abnormal Doppler study (RI)			
Umbilical artery (>95th percentile)[20]	18 (40.9%)	18 (19.6%)	<0.01
ICA (<10th percentile)*[21]	9 (20.5%)	8 (8.7%)	0.04
CPR (<10th percentile)*[21, 23]	13 (30.0%)	11 (12.0%)	<0.01
Mean uterine (>95th percentile)[20]†	15 (34.1%)	16 (17.4%)	0.04
Fetal growth restriction‡	35 (79.6%)	48 (52.2%)	<0.01
Maternal			
Gestational hypertension	20 (45.5%)	14 (15.2%)	<0.01
Pre-eclampsia	8 (18.2%)	0	<0.01
Delivery			
Gestational age at delivery (w)	36.8 (1.6)	38.6 (1.5)	<0.01
Preterm delivery (<37w)	20 (45.5%)	13 (14.1%)	<0.01
Birthweight (g)	2183 (408)	2697 (419)	<0.01
Birthweight customised centile	2.2 (0.3-6.7)	6.8 (2.8-18.0)	<0.01

<10th customised centile	42 (95.5%)	61 (66.3%)	<0.01
<3rd customised centile	29 (65.9%)	31 (33.7%)	<0.01
IOL for fetal indication	31 (70.5%)	65 (70.7%)	0.98
CS or instrumental delivery for fetal distress	13 (29.6%)	12 (13.0%)	0.02
Adverse perinatal outcome§	15 (34.1%)	14 (15.2%)	0.01

* missing n=10 (PlGF <5th centile n=5, PlGF >5th centile n=5)

† missing n=2 (PlGF <5th centile n=0, PlGF >5th centile n=2)

‡ Estimated fetal weight <3rd customised centile or abnormal Doppler (umbilical artery RI, internal carotid RI, cerebro-perfusion ratio or mean uterine artery RI)

§ Operative delivery for fetal distress and/or evidence of birth asphyxia (cord arterial pH <7.15 and base deficit >7 mEq/L, and/or Apgar score at 5 minutes <7)

PlGF, placental growth factor; EFW, estimated fetal weight; RI, resistance index; ICA, internal carotid artery; CPR, cerebral perfusion ratio; IOL, induction of labour; CS, Caesarean section.

414 **Table 3:** Low PlGF and pregnancy outcome in small for gestational age pregnancies

415 without initial features of fetal growth restriction (n=80)

	PlGF <5th centile N=17 (21.3%)	**PlGF>5th centile N=63 (78.7%)**	***P*-value**
Antenatal			
Gestational age at PlGF (weeks)	34.9 (1.2)	35.2 (1.5)	0.50
EFW (g)	2098 (263)	2230 (356)	0.16
EFW customised centile	9.8 (6.2-13.3)	8.2 (5.5-14.3)	0.34
Abnormal Doppler study (RI)			
Umbilical artery (>95th percentile)[20]	1 (5.9%)	7 (11.1%)	0.32
ICA (<10th percentile)*[21]	3 (21.4%)	5 (8.1%)	0.12
CPR (<10th percentile)*[21, 23]	2 (14.3%)	4 (6.4%)	0.23
Mean uterine artery (>95th percentile)[20]	4 (23.5%)	12 (19.1%)	0.24
Secondary fetal growth restriction†	8 (47.1%)	19 (30.2%)	0.19
Maternal			
Gestational hypertension	9 (52.9%)	8 (12.7%)	<0.01
Pre-eclampsia	1 (5.9%)	0	<0.21
Delivery			
Gestational age at delivery (weeks)	37.5 (1.3)	38.8 (1.3)	<0.01
Preterm delivery (<37 weeks)	5 (29.4%)	6 (9.5%)	0.04
Birthweight (g)	2467 (305)	2830 (382)	<0.01
Birthweight customised centile	7.6 (4.2-11.3)	9.5 (5.4-20.9)	0.05
<10th customised centile	15 (88.2%)	34 (54.0%)	0.01

<3rd customised centile	6 (35.3 %)	13 (20.6%)	0.11
IOL for fetal indication	12 (70.6%)	39 (61.9%)	0.51
CS or instrumental delivery for fetal distress	2 (11.8%)	8 (12.7%)	0.32
Adverse perinatal outcome‡	3 (17.7%)	10 (15.9%)	0.28

* missing n=4 (PlGF <5th centile n=3, PlGF>5th centile n=1)

† Abnormal Doppler RI (umbilical artery, internal carotid, cerebro-perfusion ratio or mean uterine artery)

‡ Operative delivery for fetal distress and/or evidence of birth asphyxia (cord arterial pH <7.15 and base deficit >7 mEq/L, and/or Apgar score at 5 minutes <7).

PlGF, placental growth factor; FGR, fetal growth restriction; EFW, estimated fetal weight; RI, resistance index; ICA, internal carotid artery; CPR, cerebral placental ratio; IOL, induction of labour; CS, Caesarean section.